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Functional integration across oscillation frequencies by cross-frequency phase synchronization

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Abstract

Neuronal oscillations and their inter-areal synchronization may be instrumental in regulating neuronal communication in distributed networks. Several lines of research have, however, shown that cognitive tasks engage neuronal oscillations simultaneously in multiple frequency bands that have distinct functional roles in cognitive processing. Gamma oscillations (30–120 Hz) are associated with bottom-up processing, while slower oscillations in delta (1–4 Hz), theta (4–7 Hz), alpha (8–14 Hz) and beta (14–30 Hz) frequency bands may have roles in executive or top-down controlling functions, although also other distinctions have been made. Identification of the mechanisms that integrate such spectrally distributed processing and govern neuronal communication among these networks is crucial for understanding how cognitive functions are achieved in neuronal circuits. Cross-frequency interactions among oscillations have been recognized as a likely candidate mechanism for such integration. We advance here the hypothesis that phase–phase synchronization of neuronal oscillations in two different frequency bands, cross-frequency phase synchrony (CFS), could serve to integrate, coordinate and regulate neuronal processing distributed into neuronal assemblies concurrently in multiple frequency bands. A trail of studies over the past decade has revealed the presence of CFS among cortical oscillations and linked CFS with roles in cognitive integration. We propose that CFS could connect fast and slow oscillatory networks and thereby integrate distributed cognitive functions such as representation of sensory information with attentional and executive functions.

Neuronal synchronization within limited frequency bands coordinates neuronal processing in anatomically distributed neuronal circuits

Neuronal processing is distributed into anatomically distant and functionally specialized neuronal populations. Despite such scattered representation of information and generation of functions, perceptual, cognitive and motor operations arising in healthy brains appear coherent. For example, neuronal object representations are constructed from sensory feature information in a number of specialized areas from primary to higher level sensory and associative cortices both in the visual (Riesenhuber & Poggio, 2002; Grill-Spector & Malach, 2004; Konen & Kastner, 2008) and in the auditory modalities (King & Nelken, 2009; Rauschecker & Scott, 2009; Leaver & Rauschecker, 2010) but objects are perceived and manipulated in cognition as whole rather than as collections of features. Also, cognitive functions, such as attention, working memory (WM) and awareness arise from neuronal activity in widespread and functionally modular cortical networks in posterior parietal (PPC) and prefrontal cortices (PFC) (Corbetta & Shulman, 2002; Helfrich & Knight, 2016; Leavitt *et al.*, 2017) through their interactions with the sensory systems but are nevertheless considered intractable from coherent mental states.

Neuronal (phase) synchronization is associated with millisecond-range spike-time correlations among anatomically distinct neuronal assemblies and has been suggested to be a mechanism for the coordination and regulation of neuronal processing in such anatomically distributed neuronal circuits (Singer, 2009; Fries, 2015). Such functional implications stem from two key consequences of neuronal synchronization. First, temporally coincident spikes are effective in evoking action potentials in downstream neurons and synchronization thus endows a neuronal assembly an advantage over less coherent neurons in the competition of engaging their target neurons (Singer & Gray, 1995; König *et al.*, 1996). Second, neuronal synchronization is often observed with oscillations in neuronal field and membrane potentials and thereby rhythmic modulations of neuronal excitability. Oscillations are thought to regulate neuronal communication by either facilitating it via aligned excitability windows or, conversely, inhibiting it by being out-of-phase (Fries, 2015). Neuronal synchronization and consistent phase relationships of neuronal oscillations may thus constitute a systems-level neuronal mechanism

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for achieving cognitive functions by organization, even if emergent, of scattered neuronal activity (Palva & Palva, 2012; Siegel *et al.*, 2012; Womelsdorf *et al.*, 2014b; Bastos *et al.*, 2015b; Friston *et al.*, 2015). In a multi-level mechanistic framework, synchronization would thus be a 'bottom-up causal' mechanism for achieving the cognitive functions, that is, phenomena at a higher level. Conversely, synchronization and oscillations also play a 'top-down causal' mechanistic role in modulating the underlying neuronal activity because neurons are effectively enslaved by the population activity.

Invasive local field potential (LFP) recordings from monkey (Buschman & Miller, 2007; Pipa *et al.*, 2009; Womelsdorf *et al.*, 2014a; Bastos *et al.*, 2015a) and rodent (Colgin *et al.*, 2009) brains have revealed functionally significant inter-areal neuronal synchronization both among the neocortical and hippocampal sites, respectively. A view emerging from monkey LFP data is that synchronization in gamma frequencies could support the bottom-up processing of visual information, while concurrent theta, alpha or beta synchronization could be essential for top-down/feedback communication (Buschman & Miller, 2007; Bastos *et al.*, 2015a; Voloh *et al.*, 2015).

Also, human noninvasive whole-brain recordings with electroencephalography (EEG) and magnetoencephalography (MEG) have revealed functionally significant neuronal oscillations in the human brain. In line with primate LFP data, these studies support the hypothesis that local gamma oscillations are functionally significant in the neuronal representation of sensory information that is perceived (Aru *et al.*, 2012; Michalareas *et al.*, 2016), maintained in WM (Honkanen *et al.*, 2015) and attended (Vidal *et al.*, 2006; Rouhinen *et al.*, 2013). Other lines of evidence implicate alpha oscillations in organizing attentional and executive top-down control (Palva & Palva, 2007, 2011; Klimesch *et al.*, 2008; Jensen *et al.*, 2015). However, studies on large-scale inter-areal synchronization have remained scarce and also more difficult to interpret. These studies reveal that endogenous attention is indeed associated with synchronization in the alpha (Sacchet *et al.*, 2015; Doesburg *et al.*, 2016; Lobier *et al.*, 2017) but also in the gamma (Siegel *et al.*, 2008) band. WM, in contrast, enhances oscillations concurrently in alpha, beta and gamma frequency bands in anatomically distributed networks (Palva *et al.*, 2010). Similar observations of concurrent synchronization in multiple frequency bands have also been obtained in an attentional blink study, in which multiple concurrent networks were observed for WM and attentional processing both involved in attention blink components of task (Glennon *et al.*, 2016).

Different forms of cross-frequency coupling

Several lines of evidence thus converge on showing that in a range of cognitive tasks, oscillations and network synchronization thus take place concurrently in multiple frequency bands, each with distinct functional roles and neuroanatomical sources. Hence, coherent cognitive functions would conceivably demand the integration of the distinct neuronal processes carried out concurrently in 'slow' and 'fast' (or multiple) frequency bands. Although within-frequency (1:1) synchronization may coordinate processing in *anatomically* distributed neuronal networks, it can *neither* contribute to the integration of neuronal processing distributed into distinct frequency bands *nor* mediate the interaction of bottom-up and top-down processings framed with fast and slow oscillations, respectively. The key question here is to understand which mechanisms could coordinate such spectrally distributed neuronal processing. There are two theoretically plausible phase-based interactions types that could govern the interactions between assemblies in different frequency bands and thereby accomplish cross-spectral integration and regulation of communication: 1) Cross-frequency phase synchrony (CFS), also known as *n:m* phase synchrony (Figs 1a and 2) phase-amplitude coupling (PAC) (Fig. 1b). In addition, albeit not phase-based, also cross-frequency (CF) amplitude–amplitude correlations (Fig. 1c) are one form or an outcome of cross-frequency coupling.

Within-frequency '1:1' phase synchrony is typically defined by a statistically stable (non-uniformly distributed) phase difference between two oscillations in the same frequency band. CFS is a form of phase synchrony where the stable phase difference takes place between two neuronal assemblies oscillating with an *m:n* frequency ratio (Tass *et al.*, 1998; Palva *et al.*, 2005). As the phases of both the faster and the slower oscillations are relevant for this interaction, CFS necessarily operates at the temporal accuracy of the faster oscillation. Stable CFS will be associated with consistent spike-time relationships between the neuronal assemblies in different frequency bands in a manner determined by their frequency ratio (Fig. 2a). For example, if the faster oscillation is three times faster than the slower oscillation, then the spikes of the faster oscillation may coincide with those of the slower oscillation in every third cycle of the faster

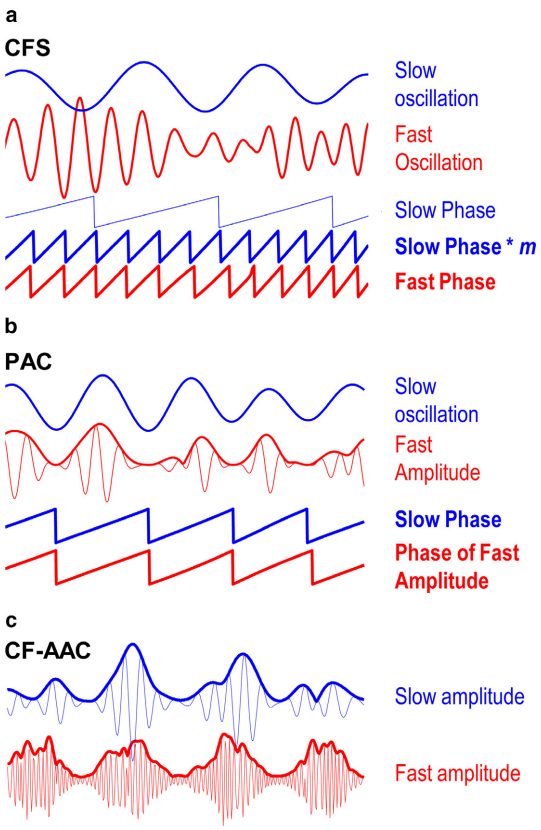

FIG. 1. Schematic of different forms of phase and amplitude cross-frequency (CF) coupling between 'slow' and 'fast' oscillations, here with $f_{fast} = 4f_{slow}$. a) CF phase synchronization (CFS) can take place between oscillations with *n:m* frequency ratio. Top rows show narrowband (filtered) real parts of these oscillations and bottom rows their phase time series. CFS can be quantified by testing whether the difference of *n:m* multiplied (here $n = 1$, $m = 4$) phases is stable (non-uniformly distributed) (Palva *et al.*, 2005). b) Phase-amplitude coupling (PAC) is the correlation between the phase of the slow oscillation and the phase of the amplitude envelope of the fast oscillation. One approach for quantifying PAC is evaluating 1:1 phase synchronization between the phase of the slow oscillation and the phase of the slow-filtered amplitude envelope of the fast oscillation (Vanhatalo *et al.*, 2004). c) CF amplitude–amplitude coupling (CF-AAC) indicates the correlation of the slow and fast amplitude envelopes.

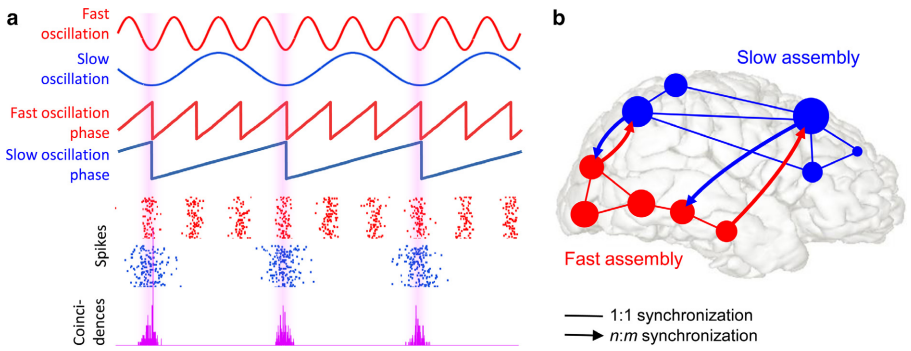

FIG. 2. Schematic for the cellular and systems-level views on CFS. a) Fast (red) and slow (blue) oscillations are coupled through 1:3 CFS with near-zero phase lag. CFS implies consistent spike-time relationships between the fast and the slow oscillations and such in-phase CFS may be associated with near-coinciding neuronal spiking which may trigger coincidence detection or burst firing mechanisms (see *Putative neuronal read-out of CFS)* and thereby incur a stronger post-synaptic impact than non-synchronous input. b) CFS may underlie the integration of fast and slow neuronal oscillatory networks by connecting key hubs of the 1:1 synchronized networks. The arrows indicate putative CFS interactions among nodes of the fast and slow oscillatory networks. Note that as CFS is a directional measure, CFS interactions can take place from slow to fast or vice versa.

oscillation. For these temporally co-localized spikes in the fast and slow assemblies, the phase lag of CFS will determine the actual spike-time relationship in a millisecond range. By this mechanism, CFS could utilize neuronal coincidence detection mechanisms and potentially serve the regulation of neuronal communication similar to 1:1 synchronization. In particular, temporally correlated neuronal spiking among the two spatially and spectrally distinct neuronal assemblies could have important computational roles given that coincident spikes and neuronal synchronization boost the impact of neuronal signals on downstream neurons (Singer & Gray, 1995; König *et al.*, 1996; Azouz & Gray, 2003; Gutig, 2014) as well as that consistent spike-timing relationships are central, for example, in spike-time-dependent plasticity (Gutig, 2014; Jaramillo & Kempter, 2017). Nevertheless, observations of CFS among neuronal oscillations have remained scarce.

PAC, on the other hand, signals the modulation of the faster oscillations' amplitude by the phase of a slower oscillation and is hence unrelated to spike synchronization. In essence, PAC reflects an interaction where the envelope but not the spike timing of fast local neuronal processing (*i.e.*, the amplitude and not the phase of the fast oscillations) is modulated by the phase of a slower oscillation. Thus unlike CFS, neither PAC nor CF amplitude–amplitude correlations are related to the phase of the faster oscillation. PAC thus reflects computational and/or modulatory mechanisms qualitatively distinct from those putatively achieved through CFS as it is uncorrelated with the spike timing of neurons engaged in the fast oscillations. In line with such a functional dissociation, a recent study by Siebenhuhner *et al.* (2016) observed distinct patterns of CFS and PAC in a VWM task. Furthermore, in contrast to the scarce observation of CFS, several studies relate PAC to different cognitive functions and have been addressed in several reviews (See (Swadlow & Gusev, 2001; Canolty & Knight, 2010) for reviews)– PAC is hence not a topic of the present review.

CF amplitude–amplitude correlations reflect yet another form of CF interactions, which refers to the coupling of amplitude envelopes between two distinct oscillation frequencies. Also, they have been observed during cognitive functions (Tass *et al.*, 1998; Palva *et al.*, 2005; de Lange *et al.*, 2008; Helfrich *et al.*, 2017) as well as shown to vary across different brain states (Stitt *et al.*, 2017). However, similar to CFS, these observations are scarce, and the functional significance of CF amplitude–amplitude coupling remains open. As neither the slow nor the fast oscillatory phases are related to this coupling, CF amplitude–amplitude correlations are independent of neuronal spike-time relationships *per se* and hence cannot carry out integrative computational roles dependent on spike-time correlations (Compare with (Singer & Gray, 1995; König *et al.*, 1996; Azouz & Gray, 2003)). Therefore, they might reflect co-modulation of excitability in the two coupled frequencies rather than direct integration of processing among fast and slow oscillatory networks.

CFS as a hypothetical mechanism contributing to cross-frequency integration

CFS is the only CF-interaction form that could be associated with consistent neuronal spike-time relationships. Hence, we propose that such coincidence of neuronal spiking associated with CFS could signal the relatedness (Singer, 1999) of two distinct neuronal oscillations in neuronal computations. While related neuronal processes could be CF-synchronized and associated with coincident neuronal spiking (Fig. 2a), unrelated neuronal processing in two distinct neuronal assemblies would not be associated with CFS and their spiking activity would be unrelated. CFS could thus allow the integration and coordination information in spectrally distributed assemblies. We further propose that CFS could thereby serve to coordinate communication across spectrally distributed large-scale networks. The structure of large-scale brain networks is frequently studied using graph theoretical tools (Bullmore & Sporns, 2009; Petersen & Sporns, 2015). Here, brain areas with many connections to other brain regions, 'hubs', are thought to be important for information processing and neuronal communication. We hypothesize that CFS could underlie the coordination and integration of neuronal processing by connecting the most central cortical hubs of the within-frequency networks (Fig. 2b). This would position CFS as a putative mechanism for coordinating processing and communication across fast and slow oscillatory networks carrying out functionally distinct computational functions. Hence, for instance, if fast network oscillations in the gamma band would underlie the representation of sensory information and slower network oscillations in the alpha bands, its attentional control, CFS between alpha- and gamma-band networks could allow the integration of these specific functions.

Observations of cross-frequency synchronization in electrophysiological data

CFS among cortical oscillations was first observed in human MEG recordings (Palva *et al.*, 2005). In this study, CFS between alpha,

beta and gamma oscillations was observed during a WM intensive mental calculation task (Fig. 3a). CFS was observed both locally within sensors and globally between different sensors located specifically over posterior parietal cortex (PPC) (Fig. 3b). Subsequent sensor-level EEG studies (Nikulin & Brismar, 2006; Sauseng *et al.*, 2008; Hamidi *et al.*, 2009; Jirsa & Muller, 2013; Nakatani *et al.*, 2013; Akiyama *et al.*, 2017) provided further support for the existence of CFS in cortical activity. Both alpha–beta and delta/theta–alpha CFS characterize human EEG data during rest (Nikulin & Brismar, 2006; Jirsa & Muller, 2013). Further, theta–gamma CFS was found to characterize visual attention supporting the idea of integration of memory and attentional processes during attended visual perception (Sauseng *et al.*, 2008). Interestingly, while alpha–beta CFS characterized visual fixation, alpha–gamma CFS characterized saccades (Nakatani *et al.*, 2013) suggesting that visual perception modulates dynamically CFS interactions. CFS has also been found between theta- and alpha-band phases during WM (Akiyama *et al.*, 2017) and during action perception between delta (1–4 Hz)- and alpha-band oscillations (Holz *et al.*, 2008) demonstrating that CFS is enhanced by a variety of cognitive functions. One of the most interesting findings was that a 10 Hz repetitive transcranial magnetic stimulation (rTMS) strengthened alpha–gamma CFS (Hamidi *et al.*, 2009). This suggests that alpha–gamma CFS is a natural interaction form in neuronal circuits that can be upregulated by a modulation of excitability. In summary, these studies support the hypothesis that CFS between oscillations in distinct frequency bands may be a novel interaction mechanism that could have a role in the integration of neuronal processing across frequencies. Furthermore, all of these early studies point to a close relationship specifically between alpha and beta or between alpha and gamma oscillations.

These sensor-level analyses of synchronization are confounded by lack of neuroanatomical insight and signal mixing, which lead to spurious observations of CFS (Nolte *et al.*, 2004; Schoffelen & Gross, 2009; Palva & Palva, 2012). Thus, although pointing to an interesting direction, the early studies did not convincingly show whether CFS is present in the neuronal activity. Recently, we estimated CFS from source-reconstructed MEG/EEG data during parametric visual WM (VWM) task (Siebenhuhner *et al.*, 2016). In an earlier study, we had found that VWM retention period is characterized by concurrent synchronization in alpha, beta and gamma frequency bands (Palva *et al.*, 2010). While synchronization in the beta and gamma bands was observed in the visual system, alpha-band synchronization was localized to frontoparietal brain areas. We now found VWM maintenance to be characterized by CFS of theta with alpha, beta and gamma oscillations as well as of high-alpha with beta and gamma oscillations (Siebenhuhner *et al.*, 2016) (Fig. 4a). Hence, theta and high-alpha-band oscillations were phase–phase synchronized with all higher frequencies with an increasing frequency ratio. Further, CFS was found among visual, frontoparietal (FP) and dorsal attention (DA) systems that are supposedly underlying the representation and attentional/executive control of VWM, respectively (Fig. 4b). This cortical localization was suggestive of the idea that CFS between fast beta/gamma and slow theta/alpha oscillations could underlie the integration of sensory and executive functions of VWM. Most important evidence supporting this idea was the observation that CFS connected the hubs of the within-frequency-synchronized networks (Fig. 4c). For comparison, also PAC was estimated during VWM task performance. PAC was indeed found, but the spectral profile was very different from that of CFS and found between theta with alpha and beta oscillations and not with alpha with beta- and gamma-band oscillations such as CFS. Also, only the strength of CFS but not PAC predicted individual VWM capacity, providing correlative indication that CFS and PAC are indeed distinct mechanism for coordinating spectrally distributed processing.

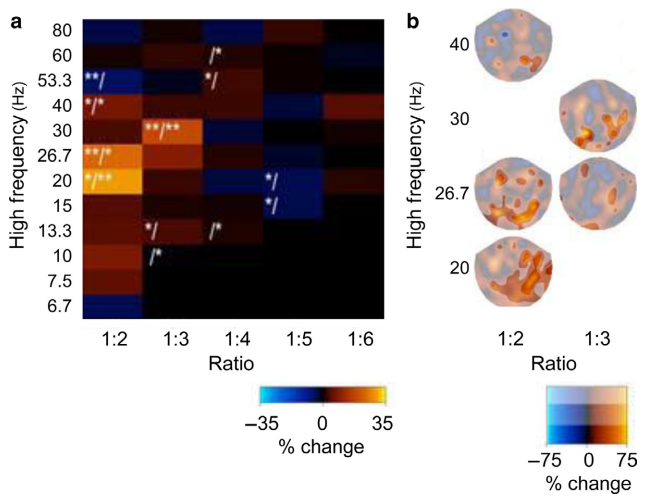

FIG. 3. CFS characterizes cortical activity in MEG sensor-level recordings during mental calculation. a) Alpha–beta and alpha–gamma CFS characterize mental calculation in MEG sensor-level analyses. The higher frequency of the pair is represented on the *y*-axis and *1:m* ratio to obtain the corresponding low frequency is represented on the *x*-axis. Color scale indicates the strength of CFS compared to rest and asterisks frequency pairs of significant CFS coupling: * < 0.05, ** < 0.01 and *** 0.001. b) The sensor layout of significantly (unmasked color scale) increased CFS with 1:2 and 1:3 frequency ratios. Modified from Palva *et al.* (2005).

Observations of cross-frequency synchronization in electrophysiological data

MEG and EEG record neuronal activity over the whole cortex and hence do not reveal whether CFS characterizes neuronal activity also in the microscale networks. Importantly, in addition to noninvasive EEG and MEG data, using intracranial EEG (iEEG) recordings from epileptic patients, CFS was also observed in the hippocampus during a memory task where the strength of CFS also correlated with memory performance (Chaieb *et al.*, 2015). This provides additional evidence that CFS is a significant interaction form both in the cortical activity and in the hippocampal activity in the human brain. Beta-gamma CFS has also been observed in monkey PPC during a choice reward task so that the strength of CFS was correlated with the choice (Hawellek *et al.*, 2016). This demonstrates that functionally significant CFS is not limited to large-scale neuronal circuits in EEG/MEG but also observed in cortical microcircuits. Similarly, CFS has been observed in layers II and III of rodent somatosensory cortex (Roopun *et al.*, 2008) and hippocampal circuits (Tort *et al.*, 2010). Thus, CFS is a significant characteristic of neuronal activity in a variety of species from rodents to humans and its strength is correlated with behavioral performance. These correlative data together show that the strength of CFS is correlated with behavioral and cognitive performance and therefore supports the idea that CFS may be a mechanism for the integration of neuronal processing distributed across frequencies. Yet further studies are needed to reveal whether CFS interactions are also causally modulating cognition and behavior. More specifically, if CFS indeed integrates neuronal processing across distinct frequencies, it should modulate neuronal firing properties, which has thus far remained unknown.

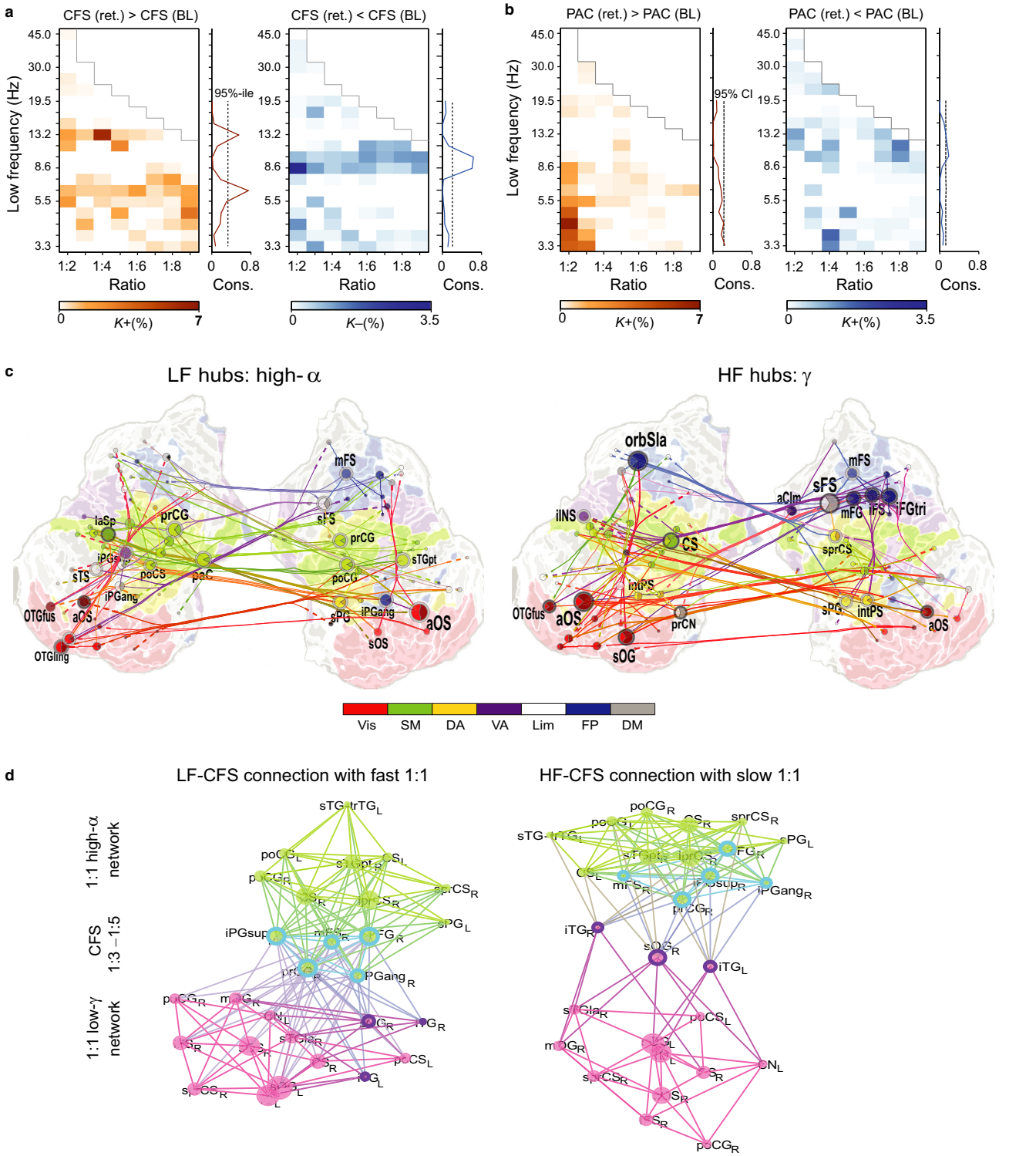

FIG. 4. CFS connects fast and slow oscillatory networks in source-reconstructed MEG/EEG data during a VWM task. a) CFS between high-alpha and beta-gamma oscillations and between theta and alpha-low-gamma oscillations characterizes maintenance of visual information in WM. Color indicates the connection density (*K*) of significant CFS connections compared to baseline. CFS was significantly consistent (Cons.) in harmonic frequency ratios compared to surrogate data. b) CFS between high-alpha and gamma oscillations was observed between the visual system and frontoparietal (FP) and dorsal attention (DA) networks. The most central connections (highest degree) of alpha (left) and gamma (right) hubs and connections displayed on flattened cortical surface. Colors indicate the Yeo-subsystem-based functional cortical parcellations (Yeo *et al.*, 2011) of nodes and connections. c) The anatomical layout of high-alpha–gamma CFS. The circles indicate the most central high-alpha-band nodes and lines their CFS connections to the gamma-band nodes. d) Simplified illustration of how CFS connects the most central nodes of the 1:1 networks. The graph shows brain areas of 1:1 phase-synchronized high-alpha-band (green) and low-gamma-band networks (pink). Blue borders indicate the brain areas that belong to the most central low-frequency CFS hubs, while violet borders indicate the brain areas that are among the most central high-frequency CFS hubs. The left column shows CFS coupling of the low-frequency CFS hubs with all of their targets in the 1:1 higher-frequency network, while the right column shows the CFS coupling of the high-frequency CFS hubs with all of their targets in the 1:1 lower-frequency network. Modified from Siebenhuhner *et al.* (2016).

Putative neuronal read-out of CFS

An important aim was to reveal what neurophysiological mechanisms could mechanistically provide a 'read-out' for cross-frequency synchronized signals. As post-synaptic potentials are non-linearly integrated, 1:1 synchronized excitatory inputs have better chances of evoking action potentials in downstream target neurons than asynchronous inputs (König *et al.*, 1996; Singer, 1999; Azouz & Gray, 2003). Hence, similar to 1:1 neuronal synchronization, also CF-synchronized inputs could hypothetically have a greater impact on post-synaptic neurons taken that post-synaptic neurons are non-linearly sensitive to spike-timing differences in the scale of CF interactions and can use this timing information as a neuronal code (König *et al.*, 1996; Azouz & Gray, 2003; Gutig, 2014). Indeed, a prior study using LFP recordings from monkey cortex shows that spiking of neuronal activity is dependent on both the beta- and the gamma-band phases in a task-dependent manner (Hawellek *et al.*, 2016). However, more evidence is required to support this hypothesis and to reveal the frequency bands between which such a coding mechanism could operate.

Another putative read-out mechanism for CF-synchronized signals is bursting activity of the layer 5 pyramidal cells. In the cortex, feed-forward sensory input terminates in the middle cortical layers, while feedback or top-down information from other parts of the cortex projects to the outer cortical layers. The most superficial cortical layer 1 neurons receiving feedback information are inhibitory neurons and because the tuft dendrites of layer 2/3 and layer 5 pyramidal neurons are positioned among layer 1 inhibitory neurons, their input shapes the firing of the main excitatory neurons of the cortex in layer 2/3 and layer 5 (Larkum *et al.*, 1999) that hence receive information from areas higher in hierarchy (Larkum, 2013). As the feed-forward information, in contrast, is relayed close to soma in the proximal apical dendrites, the layer 5 pyramidal cells receive feed-forward bottom-up and feedback top-down signals in distinct integrative compartments. Although feed-forward signals alone can evoke action potentials or burst firing, burst firing of layer 5 pyramidal cell is greatly facilitated by the feedback signals associated with back propagation of Ca^{2+} spikes causing the response to feed-forward input in the soma increase by even weak feedback signal (Palmer *et al.*, 2012; Larkum, 2013) if the inputs to apical and distal dendrites arrive simultaneously within 30 ms (Larkum *et al.*, 1999). As bursts are putatively a fundamental coding mechanism (Lisman, 1997; Izhikevich *et al.*, 2003), layer 5 pyramidal cells can effectively detect and relay the coincident bottom-up feed-forward and top-down feedback signals (Larkum *et al.*, 2004). As feed-forward inputs are thought to involve gamma-band rhythmicity (Singer, 1999; Womelsdorf *et al.*, 2007; Bosman *et al.*, 2012), while feedback/top-down signals are more likely to have periodicities in the beta and alpha frequency bands (Zarahn *et al.*, 1997; Klimesch *et al.*, 2007; Palva & Palva, 2007, 2011; Saalmann *et al.*, 2012), layer 5 pyramidal cells would be in an excellent position to underlie CFS and mediate cross-hierarchical integration. Indeed, data supporting indirectly this hypothesis have been obtained from monkey cortices using LFP recordings (Womelsdorf *et al.*, 2014a). This study shows that burst spikes are synchronized over large distances to local field potentials at beta (12–20 Hz)- and at gamma-band frequencies (Womelsdorf *et al.*, 2014a). This finding suggests that CFS interactions could indeed putatively be related to bursting; however, future studies are required to explicitly test whether neuronal bursting or facilitated spiking is associated with CFS.

Pitfalls in the CFS analyses

Although several studies point to a direction that CFS is a significant interaction form in the neuronal activity that may integrate neuronal processing distributed across frequencies, several putative pitfalls in the analyses of CFS prohibit the conclusive evidence for this claim. Specific attention should be directed to non-sinusoidal waveforms which may lead to the artificial detection of CFS without the presence of any true CFS interactions. Such artificial CFS has been proposed to explain CFS observations from neuronal data but the problem may be alleviated using appropriate surrogate methods (Schreiber & Schmitz, 2000; Scheffer-Teixeira & Tort, 2016). It is also unlikely that artificial CFS interactions would explain all observations of CFS in which the strength of CFS was correlated with behavioral performance, specifically when CFS is observed across brain regions rather than within local signals. As observations of CFS are, however, scarce, the functional significance and the contribution of non-sinusoidal waveforms to the detections of CFS interactions remain open.

In addition to controlling for confounds arising from non-sinusoidal waveforms, another important line of advancement understanding cross-frequency phase coupling in neuronal systems is the addition of directional coupling metrics. Traditional CFS analysis with PLV is purely correlative and therein comparable with other measures of 'functional' connectivity. Estimating 'effective' (Friston, 2011) cross-frequency phase coupling will be important for identifying the drivers of the effects and the true interaction networks as well as for disentangling real from spurious CFS interactions. Recently, several novel methods have been advanced for estimating effective CFS through coupling analysis triples (Rosenblum *et al.*, 2004) or formal estimation of the coupling functions (Stankovski *et al.*, 2017) where coupling functions define the strength and form of both within- and cross-frequency interactions (Stankovski *et al.*, 2017; Zhang *et al.*, 2017). Also, information theory-based methods such as the phase transfer entropy (Lobier *et al.*, 2014) can be directly applied to yield estimates of directional CF phase coupling. These lines of research will be essential for complementing functional connectivity-based approaches and for revealing how CFS may effectively regulate neuronal processing and integration.

Conclusions

We propose that cross-frequency phase synchronization (CFS) may integrate and coordinate neuronal processing distributed across frequencies and functional brain anatomy. This may be supported by CFS connecting the most central nodes of the within-frequency synchronized networks and thereby effectively regulating communication among functionally distinct neuronal assemblies. As CFS denotes phase coupling and hence spike synchronization among oscillating neuronal assemblies, CFS between neuronal oscillations may be associated with consistent spike-time relationships between the oscillating neuronal populations. Such CF-synchronized inputs could have a greater impact on the post-synaptic neuronal assemblies compared to asynchronous input, because neurons are non-linearly sensitive to spike timing (König *et al.*, 1996; Azouz & Gray, 2003; Gutig, 2014). An additional read-out for the CFS can be achieved by the layer 5 pyramidal cells. In these cells, feed-forward information, often associated with gamma-band rhythmicity, is relayed to the proximal apical dendrites, while feedback input, often associated with slower frequencies, is relayed to the distal dendrites. If inputs to proximal apical and distal dendrites of these pyramidal layer 5 cells are concurrent, *that is,* CF-synchronized taken that

inputs are oscillatory, neuronal bursting of these cells may be facilitated. Thus, two qualitatively distinct mechanisms may act as readouts for CFS and hence enable the coordination and integration of neuronal processing distributed across brain anatomy and oscillatory frequencies.

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Author contributions

SP and JMP wrote the manuscript.

Abbreviations

CF-AAC, cross-frequency amplitude–amplitude coupling; CF, cross-frequency; CFS, cross-frequency phase synchrony; DA, dorsal attention; EEG, electroencephalography; FP, frontoparietal; LFP, local field potential; MEG, magnetoencephalography; PAC, phase-amplitude coupling; PFC, prefrontal cortex; PPC, posterior parietal cortex; rTMS, repetitive transcranial magnetic stimulation; VWM, visual working memory; WM, working memory.

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